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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED OFFICE (DO/US)

PCT/SE00/00664	06 April 2000	09 April 1999
International Application Number	International Filing Date	Priority Date(s) Claimed

NEW IMPROVED FORMULATION
Title of Invention

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Applicant(s) for DO/US

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Date of Deposit JUNE 19, 2000.
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To the United States Designated Office (DO/US):

I. Accompanying this transmittal letter are certain items which are required under 35 U.S.C. 371 in order that United States National processing of the above identified International application may commence:

(X) at the expiration of the applicable time limit under PCT Articles 22 and 39(1) according to the provisions of 35 U.S.C. 371(b).

( ) as soon as possible upon receipt of this express request under 35 U.S.C. 371(f).

1. The U.S. National fee [35 U.S.C. 371(c)(1)]

a. ( ) was previously transmitted by applicant on (date)____.

b. (**X**) is submitted herewith as follows:

FOR	NO. FILED	NO. EXTRA	SMALL ENTITY RATE	FEE	or	OTHER THAN SMALL ENTITY RATE	FEE
Basic Fee	(USPTO NOT ISA OR IPEA)		////	$485	or	/////	**$970**
Total Claims	-20 =	--	x 9 =		or	x18 =	**$**
Ind. Claims	**1 - 3**	--	x 39 =		or	x78 =	**$**
(**X**) Multiple Dependent Claim Presented			+130 =		or	+260 =	**$260**
	TOTAL NATIONAL FEE		$____		or		**$1230**

i. ( ) A check in the amount of **$**___ is enclosed.

ii. (**X**) Please charge the filing fee, multiple dependent claim fee (if applicable), excess independent claims fee (if applicable), and excess total claims fee (if applicable) **to Deposit Account No. 23-1703.**

iii. (**X**) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to **Deposit Account No. 23-1703**. A duplicate copy of this sheet is enclosed.

(iv) ( ) The filing fee is not enclosed.

2. A copy of the International application as filed [35 U.S.C. 371(c)(2)]:

a. (**X**) is transmitted herewith.

b. ( ) is not required as the application was filed with the United States Receiving Office.

c. ( ) has been transmitted

i. ( ) by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed.

ii. ( ) by applicant on (date) _____.

3. A translation of the International application into the English language [35 U.S.C. 371(c)(2)]:

a. ( ) is transmitted herewith.

b. (X) is not required as the application was filed in English.

c. ( ) was previously transmitted by applicant on (date)_____.

4. Amendments to the claims of the International application under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) are transmitted herewith.

b. ( ) have been transmitted

i. ( ) by the International Bureau. Date of mailing of the amendments (from form PCT/IB/308): _____.

ii. ( ) by applicant on (date) _____.

c. (X) have not been transmitted as

i. ( ) no notification has been received that the International Searching Authority has received the Search Copy.

ii. ( ) the Search Copy was received by the International Searching Authority but the Search Report has not yet issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.

iii. ( ) applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210): .

iv. (**X**) the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

5. A Translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) is transmitted herewith.

b. ( ) is not required as the amendments were made in the English language.

c. (X) has not been transmitted for reasons indicated at point I.4.b. or c. above.

6. An executed declaration for patent application of the inventor [35 U.S.C. 371(c)(4)] complying with 35 U.S.C. 115:

a. ( ) was previously submitted by applicant on (date) _____ .

b. (X) is submitted herewith; and such oath or declaration

i. (X) is attached to the application.

ii. (**X**) identifies the application and any amendments under PCT Article 19 which were transmitted as stated in points 1.2.b. or c. and 1.4. and states that they were reviewed by the inventor as required by 37 CFR 1.70.

c. ( ) will be submitted subsequently.

II. Concerning other documents:

1. An International Search Report or Declaration under PCT Article 17(2)(a):

a. ( ) has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed

b. ( ) is not required as the application was searched by the United States International Searching Authority.

c. ( ) A copy of the International Search Report is transmitted herewith.

d. ( ) has been submitted by applicant on (date) _____.

2. A Statement of prior art under 37 CFR 1.97 and 1.98:

a. ( ) is transmitted herewith including copies of the references cited on the attached form PTO-1449.

b. ( ) will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).

c. ( ) was previously submitted by applicant on _____, in application serial no. _____.

3. (X) An Assignment is transmitted herewith for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

a. (X) Please charge the $40.00 assignment recordation fee to Deposit Account No. 23-1703.

b. ( ) Enclosed is a check in the amount of **$40**.

4. **Other document(s) or information included:**

- Copy of PCT/RO/101 - The PCT Request Form; and a
- Return postcard.

Respectfully submitted,

19 June 2000
DATE

John M. Genova
Reg. No. 32,224

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enclosures

NEW IMPROVED FORMULATION

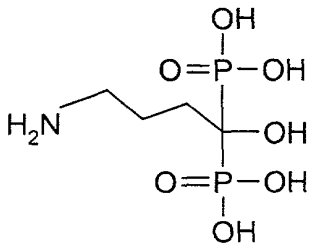
TECHNICAL FIELD

The present invention relates to pharmaceutical formulations comprising bisphosphonates. The invention also relates to a process for preparing such pharmaceutical formulations, to the use of such pharmaceutical formulations for inhibition of bone resorption and for the treatment and prevention of osteoporosis.

BACKGROUND ART

Bisphosphonates

Bisphosphonates are carbon-substituted pyrophosphate analogues that include potent inhibitors of bone resorption, such as alendronate (4-amino-1-hydroxybutylidene-1,1-biphosphonic acid) (Sato et al. (1991) J. Clin. Invest. 88, 2095-2105).



alendronate

The oral bioavailability of bisphosphonates (etidronate; clodronate; pamidronate; alendronate) in humans lies between 1% and 10% according to Lin (Bone 18, 75-85, 1996) and absorption is diminished when given with meals, especially in the presence of calcium. Therefore bisphosphonates should never be given at mealtime and never together with milk or diary products according to Fleisch (Bisphosphonates in bone disease, Stampli & Co., Bern 1993, p.50, and references cited therein). In Dowty M.E. et al, Pharm. Sci. Suppl., Vol 1, No 1: 448 (1998) the low permeability of risedronate is disclosed.

The oral bioavailability of alendronate has been studied by Gertz et al. (Clinical Pharmacology & Therapeutics, vol. 58, pp. 288-298, 1995). It was found that taking alendronate either 60 or 30 minutes before breakfast reduced bioavailability by 40% relative to a 2-hour wait before a meal. Taking alendronate either concurrently with or 2 hours after breakfast drastically (>85%) impaired availability. A practical dosing recommendation, derived from these findings was that patients should take the drug with water after an overnight fast and at least 30 min before any other food or beverage.

Moreover, the labeling information on an existing commercial formulation of alendronate (FOSAMAX®) contains a warning that the formulation, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa. This clearly shows that a solution to the problems associated with the poor and variable absorption of orally administered bisphosphonates known for a long time has not yet been found.

Consequently, there is a need for pharmaceutical formulations comprising bisphosphonates, such as alendronate, which reduces the above mentioned drawbacks and allows the patient to take the medicament more conveniently, e.g. together with food intake.

Absorption enhancers

Pharmaceutical excipients may be classified as functional or not-functional (M E Aulton: Pharmaceutics - The science of dosage form design, Churchill Livingstone 1988, Hong Kong). Non-functional excipients are, e g, binders, fillers, dryers etc and are used to fulfill pharmaceutical technology aspects of the formulation as size, hardness, appearence (e g colour) etc. Functional excipients on the other hand are utilized, e g to achieve certain types of release profiles such as immediate release, extended release, controlled release etc by the use of rapidly or slowly hydrating, swelling, eroding, etc polymer materials; to achieve fast dissolution of the drug by incorporating surface active substances; to achieve control of the pH in the formulation or in the immediate environment of the drug by the usage of buffers in the formulation; etc.

Another important aspect of excipients is the influence from functional excipients on the biological environment that can be obtained with certain substances, often called enhancers in the literature, by for example changing the permeability of the biological membrane, to inhibit complex formation with biological substances present (e g proteins, lipids, bile salt, ions), etc. The rational for the use of such excipients is then to achieve, e g higher availability, less variation in absorption due to, e g food interactions (Charman WN et al. J Pharm Res 86 (3): 269-282 (1997)) avoidance of instability in GI-environment, to diminish drug influence on membrane integrity etc. Comprehensive reviews on the effect of enhancer agents and their use in pharmaceutical formulations have been presented by E J van Hoogdalem et al (Pharm Theor vol 44, 407-443 (1989)); by S Muranishi et al (Crit Rev Ther Drug Carrier Syst vol 7, 1-33 (1990)); by E S Swenson and W J Curatolo (Adv Drug Deliv Rev vol 8, 39-92 (1998)); in drug Absorption Enhancement (Ed: A B G de Boer, Harwood Academic Publishers 1994); in Baughman RA et al Circulation 98 (16): 1610-1615 (1998); in Bai JP et al, Crit Rev Therap Drug Carrier Syst 12(4): 339-371 (1995); in Bowe CL et al, Proc Nat Acad Sci 94 (22): 12218-23 (1997); in Chao AC et al, J Pharm Sci 87(11): 1395-1399 (1998); in Chao AC et al, J Drug Targeting 6(1): 37-43 (1998); and in Fix JA. J Pharm Sci 85(12) 1282-1285 (1996).

In many circumstances the enhancers combine several different effects. However, the degree of influence on the biological environment is seldom known á priori, and mechanisms behind the effects are obscure and difficult to ascertain in-vivo. The different types of such functional excipients includes e g lipids, chelators, and polymers which all may act, e g by preventing or enhancing complexation with species from the biological environment (e g proteins, bile salts, lipids, ions like Ca^{2+} etc), by influencing the membrane permeability in a reversible or irreversible manner, by presenting the drug in small particulate form and thereby avoiding high local concentrations that might be irritating near the membranes of the drug, etc.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that the absorption of bisphosphonates can be substantially improved by incorporating one or more additives in pharmaceutical formulations containing bisphosphonates. The use of additives as enhancers will result in positive advantageous effects, such as enhanced and/or less variable absorption when bisphosphonates, e.g. alendronate, is given by different administration routes, such as the oral, the rectal, the buccal, the nasal and the pulmonary route. It will allow the patient to take the medicament more conveniently, e.g. together with food intake. It will also reduce side-effects as local irritation of, e g the upper gastrointestinal mucosa.

Therefore, the present invention provides a pharmaceutical formulation comprising at least one bisphosphonate and one or more additives selected from the group consisting of

- a surfactant, such as a nonionic surfactant, e.g., a sorbitan ester (Span series), a polysorbate (Tween series), a poloxyethylated glycol monoether (like the Brij series), a polyoxylated alkyl ester (Myrj series), a polyoxyethylated alkyl phenol (like the Triton series), an alkyl glucoside, like sugar glycosides, e.g., dodecylmaltoside, sugar fatty acid esters, e.g. sucrose laurate, sucrose monostearate and saponins;
- an ampholytic surfactant, e.g., a betaine;
- an anionic surfactant, e.g., a sulphated fatty alcohol, a sulphated polyoxyethylated - alcohol, others like dioctyl sulphosuccinate;
- a cationic surfactant, e.g., an ammonium compound;
- a bile salt, such as a dihydroxy bile salt like sodium deoxycholate, a trihydroxy bile salt like sodium glycocholate and fusidates, e.g., sodium dihydrofusidate;
- a soap and a fatty acid, and a salt thereof, e.g. octanoic acid, decanoic acid and sodium decanoate;
- a lipid (with the exception of those dislosed in PCT application no. SE98/01790), such as a phospholipid, e.g., DPPC and DMPC;
- an oil, e.g., soy bean oil and sunflower oil;
- an enamine, such as DL-phenylanaline and ethylacetoacetate enamine;
- a chelating agent, e.g., EDTA, EGTA, and citric acid;
- a phenothiazine, such as chlorpromazine;

- a fatty acid derivative of carnitine and peptides, e.g., palmitoyl-DL-carnitine;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative, such as DL -a-glycerophosphate and 3-amino-1-hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate;
- a product from Maillard reactions, i.e. a product obtained by reacting sugars with amino acids, e.g., a compound from a glucoselysine reaction;
- a polymer, such as a polyacrylic acid, e.g., Carbopol®, polycarbophil;
- a chitosan and a chitosan derivative; and
- a block copolymer, e.g., a poloxamer, poloxamine, and meroxapol.
- a biodegradable polymer, e g polyactic acid, polyglycolic acid, and copolymers of these.

Suitable intended combinations of the enhancing agents are, but are not limited to:

Lipids (also those disclosed in PCT application no. SE 98/01790) and surfactants, eg monoolein and sodium taurocholate, monoolein and Tween 80 (polyoxyethylene (20) sorbitan mono-oleate, also namned polysorbate 80);

Lipids of non-phospholipids character (also those disclosed in SE 98/01790) and phospholipids, e g medium chain glycerides and lecithins;

Lipids (also those disclosed in SE 98/01790) and block copolymers, e g monoolein and Pluronic F 127 (which is the triblock copolymer poloxamer 407 of polyoxyethylene/polyoxypropylene/polyoxyehylene);

Surfactants and oils, e g sucrose fatty acid esters and soy bean oil; and

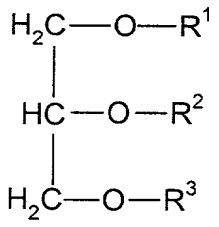
Polymers and lipids, e g polycarbophil and monoolein.

The combinations might be in the form of emulsions and microemulsions comprising e g monoolein/triglyceride/water or isopropyl myristate/lecithin/water.

Preferred additives of the invention are

- nonionic surfactants, such as sugar glycosides and sugar fatty acid esters;
- lipids, such as a phospholipid e g DPPC and DMPC;
- an oil, such as soy bean oil and sunflower oil;
- a chelating agent, e g EDTA, EGTA, citric acid;
- a fatty acid derivative of carnitine or a peptide; e.g. palmitoyl-DL-carnitine;
- polymer, such as polyacrylic acid, e g Carbopol, polycarbophil
- a block copolymer, e g a poloxamer, poloxamine and meroxapol;
- a saponin;
- the combinations listed above.

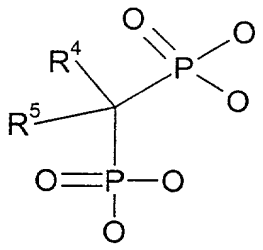
Lipids referred to above as disclosed in PCT application no. SE 98/01790 are a medium chain glyceride or a mixture of medium chain glycerides, particularly those having the formula



wherein R^1, R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms, provided that at least one or R^1, R^2 and R^3 is an alkanoyl group.

The dosage form used may be a solid, semisolid or liquid preparation prepared by techniques which are known *per se*. Usually the active substance will constitute between 0.001% and 99% by weight of the preparation, preferably 0.003 to 1.3 % by weight, most preferably 0.1 to 1%.

Preferably, the bisphosphonate has the general formula II



II

wherein

R^4 is H, OH or Cl; and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;

(b) halogen;

(c) arylthio, preferably chlorosubstituted;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

Alkyl groups in alkylamino and dialkylamino may have 1 to 5 carbon atoms and may be combined independently in the dialkylamino group.

The term "heterocyclyl" means a saturated or unsaturated 5 to 7- membered heterocyclic group with one or two rings and 1 to 3 heteroatoms, independently chosen from N, O and S.

Unless otherwise stated or indicated, the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups, such as naphtyl.

The term "substituted aryl" denotes an aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, aryl or cyano groups.

Compounds of the formula II include:
4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate),
N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (mildronate,olpadronate),
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate),
1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate),
1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate),
1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid,
1-hydroxy-2-(1-imidazolyl)etylidene-1,1-bisphosphonic acid (zoledronate),
1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid (minodronate),
1-(4-chlorophenylthio)methylidene-1,1- bisphosphonic acid (tiludronate),
1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate),
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate)
and pharmaceutically acceptable salts there of.

The most preferred compounds of the formula II are 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate) and its pharmaceutically acceptable salts.

In a preferred form, the pharmaceutical formulation according to the invention is adapted for oral administration and may be given during fasted or fed conditions.

In the preparation of pharmaceutical formulations according to the invention in the form of dosage units for oral administration, the bisphosphonate and the absorption enhancing agent may be filled into soft or hard gelatine or cellulose capsules; mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient; with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate

and polyethylene glycol waxes. The mixture is then processed into particulate forms, granules or pressed into tablets.

In one embodiment of the invention the bisphosphonate and the additive is mixed into a suitable form considering that a particulate (solid, semisolid or liquid) form might be preferably chosen to avoid the presentation of the drug in high local concentrations that might be irritating at the mucosal membranes. Such particulate forms can be obtained by well known procedures, such as dispersing the bisphosphonate as a micronised powder (< 10 μm) in a suitable medium like sesam oil, soya oil etc, or by forming a carrier/drug system in particulate form. Micronised bisphosphonates or carrier/drug systems can be prepared by techniques such as but not limited to dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, spray freeze drying, electrospraying, supercritical crystallisation (RESS or GAS methods), emulsion solvent evaporation, emulsion solvent extraction and emulsion solvent diffusion.

This suspension of the bisphosphonate in oil or the carrier/bisphosphonate system is then administered orally as a suspension or in capsules.

Suitable daily doses of bisphosphonates in therapeutic treatment of humans are about 0.001 to 100 mg/kg body weight at peroral administration, preferably 0.001 to 10 mg/kg, most preferably 0.005 to 0.3 mg/kg.

The enhancing agent, or the combination of enhancing agents, and a suitable carrier or non-functional excipients when needed will constitute between 0.1 to 99.9% by weight of the preparation, preferably between 80% to 99.9% by weight.

The pharmaceutical formulations according to the invention are useful for inhibiting bone resorption and thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis. The pharmaceutical formulations according to the invention are further useful for the

treatment of hypercalcaemia. Consequently, the use of the said pharmaceutical formulations for treating these conditions are additional aspects of the invention.

In another aspect the invention provides a process for the preparation of a pharmaceutical formulation according to the invention, said process comprising forming a mixture of (i) bisphosphonate, (ii) an additive, and (iii) a pharmaceutically acceptable carrier.

In a further aspect the invention provides the use of bisphosphonate in conjunction with an absorption enhancing agent for the manufacture of a medicament for the inhibition of bone resorption, or thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis. Preferably, the said medicament is adapted for oral administration.

In yet a further aspect the invention provides a method for the inhibition of bone resorption, or thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis, which method comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to the invention. Preferably, the said pharmaceutical formulation is administered orally.

Biological evaluation

The effectiveness of formulations according to the present invention to prevent bone loss has been analyzed in studies using intact young growing rat model, developed and well established to predict the effectiveness of bisphosphonates in later clinical practise.

Results

ED_{50} values obtained in the intact rat model show that orally administered formulations according to the invention that have been tested are more potent than equimolar bisphosphonate alone.

In a 14-day study of intact young growing rats a clear dose-response effect of enhancer was found. No effects were found for bisphosphonate in saline and given per os.

The effects on bone density obtained with enhancer/bisphosphonate was similar to what was obtained with bisphosphonate given subcutaneously, while no effect was found for bisphosphonate in saline given per os.

All rats appeared normal and gained normal weight.

Conclusions

The rat studies strongly support the concept that enhancers as suggested in the present specification can increase the oral bioavailability of a bisphosphonate as disclosed in the present specification even in the presence of food.

Examples

Examples of pharmaceutical formulations according to the invention:

Formulation 1

Alendronate	2.3 mg
Caprylic acid, sodium salt	11.5 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

Approx. 2.3 mg alendronate and 11.5 mg caprylic acid was dissolved in buffer and pH adjusted to 7.5 using sodium hydroxide.

Formulation 2

Alendronate	2.3 mg
Monoolein	11.5 mg
Tween 80	11.5 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

Approx. 2.3 mg alendronate and 11.5 mg monoolein was dissolved in buffer containing Tween 80 and pH adjusted to 7.5 using sodium hydroxide.

Formulation 3

Alendronate	2.3 mg
Quil A	11.5 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

Approx. 2.3 mg alendronate and 50 mg Quil A was dissolved in buffer and pH adjusted to 7.5 using sodium hydroxide.

Formulation 4

Alendronate	2.3 mg
Carbopol 934P	5.0 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

Approx. 2.3 mg alendronate and 5.0 mg Carbopol was mixed with buffer to form a dispersion and pH adjusted to 7.5 using sodium hydroxide.

Formulation 5

Alendronate	2.3 mg
Carbopol 934P	15.0 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

Approx. 2.3 mg alendronate and 15.0 mg Carbopol was mixed with buffer to form a dispersion and pH adjusted to 7.5 using sodium hydroxide.

Formulation 6

Alendronate	2.3 mg
Isopropylmyristate	630 mg
Lecithin (Epicuron 200)	270 mg
50 mM Tris with 100 mM NaCl (buffer)	100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of isopropylmyristate and lecithin (70/30 w/w) while vortexing.

Formulation 7

Alendronate	2.3 mg
Isopropylmyristate	450 mg
Tween 21	450 mg

50 mM Tris with 100 mM NaCl (buffer)	100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of isopropylmyristate and Tween 21 (50/50 w/w) while vortexing.

Formulation 8

Alendronate	2.3 mg
Monoolein	630 mg
Soybean triglycerides	270 mg
50 mM Tris with 100 mM NaCl (buffer)	100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of monoolein and soybean triglycerides (70/30 w/w) while vortexing.

Formulation 9

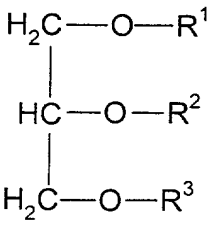
Alendronate	2.3 mg
Soybean triglycerides	1.0 g

2.3 mg alendronate was added to soybean triglycerides and micronized using ultrasonication while cooling on ice.

CLAIMS

1. A pharmaceutical formulation comprising at least one bisphosphonate and one or more of an additive agent, said additive agent being present in an amount sufficient to provide an enhanced absorption of the bisphosphonate, and said additive being a substance selected from the group consisting of

- a surfactant;
- an ampholytic surfactant;
- an anionic surfactant;
- a cationic surfactant;
- a bile salt;
- a soap and a fatty acid, and a salt thereof;
- a lipid with the exception of a medium chain glyceride or a mixture of medium chain glycerides having the formula



wherein R^1, R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms, provided that at least one or R^1, R^2 and R^3 is an alkanoyl group.

- an oil;
- an enamine;
- a chelating agent;
- a phenothiazine;
- a fatty acid derivative of carnitine or a peptide;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative, such as DL -a-glycerophosphate and 3-amino-1-hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate;

- a product from Maillard reactions;
- a polymer, such as a block copolymer and a biodegradable polymer;
- a chitosan and a chitosan derivative;

2. A pharmaceutical formulation according to claim 1, wherein the additive is a nonionic surfactant.

3. A pharmaceutical formulation according to claim 2, wherein the nonionic surfactant is a sugar glycoside or a sugar fatty acid ester.

4. A pharmaceutical formulation according to claim 1, wherein the additive is a lipid.

5. A pharmaceutical formulation according to claim 4, wherein the lipid is a phospholipid.

6. A pharmaceutical formulation according to claim 1, wherein the additive is an oil.

7. A pharmaceutical formulation according to claim 6, wherein the oil is soy bean oil or sunflower oil.

8. A pharmaceutical formulation according to claim 1, wherein the additive is a chelating agent.

9. A pharmaceutical formulation according to claim 8, wherein the chelating agent is EDTA, EGTA or citric acid.

10. A pharmaceutical formulation according to claim 1, wherein the additive is a fatty acid derivative of carnitine or a peptide.

11. A pharmaceutical formulation according to claim 10, wherein the additive of the fatty acid derivative of carnitine or a peptide is palmitoyl-DL-carnitine.

12. A pharmaceutical formulation according to claim 1, wherein the additive is a polymer.

13. A pharmaceutical formulation according to claim 12, wherein the polymer is a polyacrylic acid.

14. A pharmaceutical formulation according to claim 1, wherein the additive is a block copolymer.

15. A pharmaceutical formulation according to claim 14, wherein the block copolymer is a poloxamer, a poloxamine or meroxapol.

16. A pharmaceutical formulation according to claim 1, wherein the additive is a saponin.

17. A pharmaceutical formulation according to claim 1, wherein the additive is a biodegradable polymer.

18. A pharmaceutical formulation according to claim 17, wherein the biodegradable polymer is polyactid acid or polyglycolic acid.

19. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a surfactant.

20. A pharmaceutical formulation according to claim 19, wherein the combination of the lipid and the surfactant is monoolein and sodium taurocholate, or monoolein and Tween 80.

21. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid of non-phospholipid character and a phospholipid.

22. A pharmaceutical formulation according to claim 21, wherein the combination of the lipid of non-phospholipid character and the phospholipid is a medium chain glyceride and a lecithin.

23. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a block copolymer.

24. A pharmaceutical formulation according to claim 23, wherein the combination of the lipid and the block copolymer is monoolein and Pluronic F 127.

25. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a surfactant and an oil.

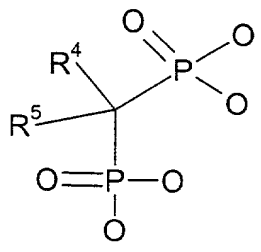
26. A pharmaceutical formulation according to claim 25, wherein the combination of the surfactant and the oil is a sucrose fatty acid ester and soy bean oil.

27. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a polymer and a lipid.

28. A pharmaceutical formulation according to claim 27, wherein the combination of the polymer and the lipid is polycarbophil and monoolein.

29. A pharmaceutical formulation according to claim 1, wherein the combination of additives is chosen to form an emulsion or a microemulsion.

30. A pharmaceutical formulation according to any one of claims 1 to 29 wherein the said bisphosphonate has the formula II



II

wherein

R^4 is H, OH or Cl, and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;

(b) halogen;

(c) arylthio or chlorosubstituted arylthio;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

31. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R^4 is H or OH and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

32. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R^4 is OH and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

33. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate), N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (mildronate,olpadronate), 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate), 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate), 1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate), 1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid, 1-hydroxy-2-(1-imidazolyl)etylidene-1,1-bisphosphonic acid (zoledronate), 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid (minodronate), 1-(4-chlorophenylthio)methylidene-1,1- bisphosphonic acid (tiludronate), 1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate), 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate) and pharmaceutically acceptable salts there of.

34. A pharmaceutical formulation according to claim 33 wherein the bisphosphonate is alendronate (4-amino-1-hydroxybutylidene-1,1-biphosphonic acid) or pharmaceutically acceptable salts there of.

35. A pharmaceutical formulation according to any one of claims 1 to 34 which is adapted for oral administration.

36. A pharmaceutical formulation according to any one of claims 1-35 which is adapted for non colonic delivery.

37. A pharmaceutical formulation according to any one of claims 1 to 36 for inhibiting bone resorption.

38. A pharmaceutical formulation according to any one of claims 1 to 36 for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

39. A pharmaceutical formulation according to any of the preceeding claims wherein the formulation is in particulate form.

40. A pharmaceutical formulation according to claim 39 wherein the particulate form is solid or semisolid.

41. A pharmaceutical formulation according to any of claims 39 and 40 wherein the bisphosphone is in the form of micronized powder.

42. A process for the preparation of a pharmaceutical formulation according to any one of claims 1 to 40, comprising forming a mixture of (i) at least one bisphosphonate, (ii) an additive and (iii) a pharmaceutically acceptable carrier.

43. The use of a pharmaceutical formulation according to any one of claims 1 to 41 for the manufacture of a medicament for the inhibition of bone resorption.

44. The use of a pharmaceutical formulation according to any one of claims 1 to 41 for the manufacture of a medicament for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, or cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

45. A method for inhibition of bone resorption which comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 41.

46. A method for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis,which comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 41.

Docket Number (Optional) H 2160-1P US

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW IMPROVED FORMULATION

the specification of which is attached hereto unless the following box is checked:

☒ was filed on 6 April 2000 as United States Application Number or PCT International Application Number PCT/SE00/00664 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

			Priority Not Claimed
9901272-6 (Number)	Sweden (Country)	9 April 1999 (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country	_____ (Day(Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

_____ (Application Number) _____ (Filing Date)

_____ (Application Number _____ (Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Dimitrios Drivas, Reg. No. 32,218; Cecilia O'Brien Lofters, Reg. No. 33,434; Warren S. Heit, Reg. No. 36,828; David Bender, Reg. No. 35,445; John M. Genova, Reg. No. 32,224; Richard J. Sterner, Reg. No. 35,372; Hans-Peter G. Hoffmann, Reg. No. 37,352; Leslie Morioka, Reg. No. 40,304; John Scheibeler, Reg. No. 35,346; Thelma A. Chen Cleland, Reg. No. 40,948, Jean E. Shimotake, Reg. No. 36,273; Jeff Oelke, Reg. No. 37,409; Chase Romick, Reg. No. 45,051; and Louis S. Silvestri, Reg. No. 45,108 of the firm of WHITE & CASE LLP, with offices at 1155 Avenue of the Americas, New York, New York 10036,

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Fifth inventor's signature _____ Date _____

Residence Address _____ Citizenship _____

Post Office Address _____

Additional inventors are being named on separately numbered sheets attached hereto.